

Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-64 are pending in the application, with 7, 13, 19, 27, 35, 42, and 49 being the independent claims.

Based on the following Remarks, the Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and they be withdrawn.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 1-64 under 35 U.S.C. § 103 as allegedly having been obvious from Tye (U.S. Patent No. 4,529,719) in view of Bucci *et al.* (U.S. Patent No. 5,290,919) and Rauch *et al.* (U.S. Patent No. 5,084,558). The Applicant asserts that the claims would not have been obvious from Tye, Bucci, Rauch, or any combination thereof, and thus respectfully requests reconsideration in view of the following arguments.

1. Claims 1-64: No teaching of a "non-pyrogenic, endotoxin-free, oxygen-free" hemoglobin

All currently pending claims recite a "non-pyrogenic, endotoxin-free, oxygen-free, stroma-free, cross-linked tetrameric hemoglobin" (or if not "oxygen-free," then the step of "removing oxygen from hemoglobin"). In order for the Examiner's rejection to stand, all of these limitations must be taught or suggested in the cited art. The Applicant respectfully submits that the cited art does not teach a hemoglobin that is non-pyrogenic, endotoxin-free, and oxygen-free.

The Examiner notes that the Tye '719 patent teaches "a stroma free tense state tetrameric hemoglobin cross linked with bis(3,5-dibromosalicyl)-fumerate and modified with pyridoxal-5'-phosphate." (Paper no. 11 at p. 2). However, the Examiner notes major differences between the

Tye '719 patent and the present invention: "the reference does not teach removing endotoxin from preparation containing red blood cells, removing oxygen from red blood cells, and lysing red blood cells." (Paper no. 11 at p. 3).

However, the Examiner purports to find the deficiencies of the Tye '719 patent in the Bucci '919 and Rauch '518 patents. Regarding the Bucci teachings, the Examiner writes that Bucci "states that it is necessary to have the hemoglobin in deoxy form for the pyridoxylation with pyridoxal-5'-phosphate." (Paper no. 11 at p. 3). The Applicant respectfully disputes the Examiner's reading of Bucci. The Examiner cites col. 3, lines 50-64 to support his allegations. The Examiner interprets the cited passage as teaching "suspension of red blood cells with a reducing agent to maintain the solution in deoxy form." However, reading the cited passage demonstrates that what Bucci is discussing is the need to decrease the *affinity* of hemoglobin for oxygen (i.e., how tightly hemoglobin binds oxygen) in environments outside red blood cells. (Incidentally, the Applicant finds no teaching of a reducing agent in the cited passage.) As explained in more detail in Bucci at col. 1, lines 45-48, "outside of the red blood cells, hemoglobin has a high affinity for oxygen which, *in vivo*, would prevent the release, i.e., the transport, of oxygen from hemoglobin to the tissues." What Bucci is discussing in the passages cited by the Examiner (col. 3, lines 50-64) is a way to decrease the affinity of hemoglobin for oxygen so that it can release oxygen *in vivo*. It has nothing to do with deoxygenating hemoglobin in the sense of removing substantially all of the oxygen in a sample of hemoglobin.

The Applicant respectfully submits that the Examiner most likely intended to refer to Bucci at col. 9, lines 50-56 (not col. 3). It is here that Bucci mentions that "the reagent of the present invention is added to the hemoglobin which is kept in a closed container under nitrogen or some other inert gas at atmospheric pressure. Residual oxygen is eliminated by the addition of

oxygen-absorbing agents...". However, the Applicant submits that this disclosure of Bucci is insufficient to provide a teaching of an "oxygen-free" hemoglobin. As noted in the present specification at page 14: "most investigators erroneously believe that merely by bubbling nitrogen through the solution for 15-30 minutes they will have removed substantially all of the oxygen present." Without a measurement to ensure that Bucci's preparations are actually "oxygen-free," Bucci cannot be said to teach this aspect of the claims. Thus Bucci neither discloses nor suggests an "oxygen-free" hemoglobin.

Finally, the Examiner alleges that the Rausch '558 patent supplies the "endotoxin-free" limitation of the claims at issue. However, the Examiner has not alleged any motivation to combine the teachings of Rausch with those of Tye and Bucci. As established above, Bucci lacks a hemoglobin that is "non-pyrogenic," "endotoxin-free," and "oxygen-free;" and Tye lacks a hemoglobin that is "non-pyrogenic" and "endotoxin-free."

But Rausch cannot be used in combination with Tye and Bucci because Rausch teaches away from the Tye approach. The Background section of the Rausch patent sets forth a summary of the Tye '719 patent's stromal free, cross-linked hemoglobin (Rausch, col. 5, lines 15-48), then states that "in spite of the recent advances in the preparation of 'stromal-free,' cross-linked hemoglobin origin blood substitutes, the need has continued to exist for a blood substitute which is substantially free of endotoxins, phospholipids, and non-hemoglobin proteins ...". Apparently, Rausch considers the approach in the Tye patent to be inadequate.

The Applicant has established that Tye, Bucci, and Rausch should not be combined in the manner suggested by the Examiner. Individually, these references do not teach or suggest the presently claimed invention. Tye and Bucci neither teach nor suggest a "non-pyrogenic," "endotoxin-free" hemoglobin and Rausch does not teach or suggest at least "oxygen-free"

hemoglobin. The Applicant thus requests reconsideration of the rejections of all claims, and that the rejections be withdrawn.

2. *Claims 19-26, 35-41, and 51-57: No teaching of "removing oxygen from [a] preparation containing red blood cells"*

Claims 19-26, 35-41, and 51-57 recite, *inter alia*, "removing oxygen from [a] preparation containing red blood cells". The Examiner acknowledges that the Tye patent does not teach this: "The difference between the [Tye patent] and the instant application is that the [Tye patent] does not teach ... removing oxygen from red blood cells...". (Paper no. 11 at page 3).

Bucci likewise does not teach "removing oxygen from [a] preparation containing red blood cells." As set forth in section 1 above, Bucci does not teach an oxygen-free hemoglobin. But to the extent that Bucci removes oxygen at all, it is not from a preparation containing red blood cells, but rather from a preparation containing hemoglobin. In fact, Bucci explicitly teaches removing stromal material first (Bucci, col. 8, line 50 – col. 9, line 23), *before* removing some of the oxygen from the preparation and cross linking the hemoglobin (Bucci, col. 9, lines 25-56). Thus Bucci can be read to teach away from removing oxygen from red blood cells, or at least cannot be read to teach this step.

Nor does Rausch teach "removing oxygen from [a] preparation containing red blood cells," and the Examiner has not alleged that Rausch teaches such a step. The Applicant has thus established that the Tye patent, the Bucci patent, and the Rausch patent have no teachings of a method involving the step of "removing oxygen from [a] preparation containing red blood cells." The cited references, either individually or in combination, neither disclose nor suggest this step. The Applicant thus respectfully requests reconsideration of the rejections of claims 19-26, 35-41, and 51-57, and that the rejections be withdrawn.

3. *Claims 22, 30, 38, 45, 54, and 61: No teaching of "washing surfaces and equipment that will come into contact with the cross-linked hemoglobin with a dilute solution of a hemoglobin."*

Claims 22, 30, 38, 45, 54, and 61 recite, *inter alia*, "washing surfaces and equipment that will come into contact with the cross-linked hemoglobin with a dilute solution of a hemoglobin."

The Examiner has not alleged that any of the cited references teaches or suggests this step. The washing step is detailed in the specification at page 13. The Applicant respectfully submits that his novel method for removing and eliminating endotoxins by washing with a solution of hemoglobin would not have been obvious to those skilled in the art. The Applicant thus requests reconsideration of the rejections of claims 22, 30, 38, 45, 54, and 61, and that the rejections be withdrawn.

4. *Claims 23, 28, 31, 36, 37, 39, 43, 44, 46-48, 55, 59, and 62: No teaching of "centrifuging a solution of [red blood] cells under vacuum at a speed sufficient to produce a force greater than the surface tension of the solution," or "centrifuging ... red blood cells under a vacuum sufficient to remove oxygen from the preparation."*

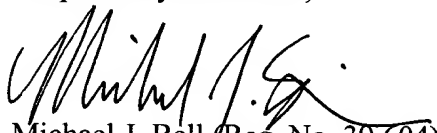
Claims 23, 28, 31, 36, 37, 39, 43, 44, 46-48, 55, 59, and 62 recite, *inter alia*, either the step of "centrifuging a solution of [red blood] cells under vacuum at a speed sufficient to produce a force greater than the surface tension of the solution," or the step of "centrifuging ... red blood cells under a vacuum sufficient to remove oxygen from the preparation." The Examiner has not alleged that any of the cited references teaches or suggests either of these steps. The centrifuging under vacuum step is detailed in the specification at page 14. The Applicant respectfully submits that his novel method for removing oxygen from red blood cells or from hemoglobin preparations by centrifuging under vacuum would not have been obvious to those skilled in the art. The Applicant thus requests reconsideration of the rejections of claims 23, 28, 31, 36, 37, 39, 43, 44, 46-48, 55, 59, and 62, and that the rejections be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. The Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. The Applicant believes that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Michael J. Bell", with a stylized flourish at the end.

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